STIM1 gene

stromal interaction molecule 1

Normal Function

The *STIM1* gene provides instructions for making a protein called stromal interaction molecule 1 (STIM1). The STIM1 protein is involved in controlling the entry of positively charged calcium atoms (calcium ions) into cells when levels of the ions are low, specifically through channels called calcium-release activated calcium (CRAC) channels. The flow of calcium ions through CRAC channels triggers signaling within cells that plays a role in many cellular functions including control of gene activity, cell growth and division, and immune function.

STIM1 is found in the membrane of a cellular structure called the endoplasmic reticulum (ER), which, among other functions, stores calcium in cells. STIM1 recognizes when calcium levels in the ER are low and stimulates changes in the cell that allow STIM1 to attach (bind) to a protein called ORAI1 in the cell membrane. This protein, which is part of the CRAC channel, forms a hole (pore) in the cell membrane through which calcium ions can flow. STIM1 binding triggers the flow of calcium ions into the cell through the channel. STIM1 also likely plays a role in the process that stops the flow of calcium ions when enough calcium has entered.

STIM1 is also found in the sarcoplasmic reticulum, a structure similar to the ER that is found in muscle cells. This structure plays a major role in muscle contraction and relaxation by storing and releasing calcium ions. The STIM1 protein is thought to help replenish calcium stores in the sarcoplasmic reticulum through CRAC channels. It may also be involved in the release of calcium ions from the sarcoplasmic reticulum, which stimulates muscle contraction.

Health Conditions Related to Genetic Changes

Stormorken syndrome

A mutation in the *STIM1* gene causes Stormorken syndrome, a rare condition characterized by a low number of platelets (thrombocytopenia) and consequent bleeding problems, a muscle disorder called tubular aggregate myopathy (described below), and other abnormalities. The mutation involved in this condition changes a single protein building block (amino acid) in the STIM1 protein, replacing the amino acid arginine with the amino acid tryptophan at protein position 304 (written as Arg304Trp or R304W). This change occurs in a region of the protein that is thought to be involved in keeping it turned off when calcium ion levels are high. As a result of this change, the altered STIM1 protein is constantly turned on (constitutively

active), continually stimulating calcium ion entry through CRAC channels regardless of ion levels in the ER. Because the genetic change enhances the activity of the protein, it is described as a "gain-of-function" mutation. Researchers suggest that the abnormal ion flow in platelets causes the cells to die earlier than usual, leading to thrombocytopenia and bleeding problems in people with Stormorken syndrome. It is unknown how constitutively active STIM1 leads to the other features of the disorder.

tubular aggregate myopathy

At least five gain-of-function mutations cause tubular aggregate myopathy without the other features of Stormorken syndrome (described above). In this disorder, proteins build up abnormally in muscle cells, forming clumps of tube-like structures called tubular aggregates. Tubular aggregate myopathy causes muscle pain, cramping, or weakness that worsens over time. The mutations involved in this condition change single amino acids in STIM1, specifically in the region of the protein used for sensing calcium ion levels. Like the gain-of-function mutation that causes Stormorken syndrome, these mutations lead to production of a constitutively active STIM1 protein that continually stimulates calcium ion flow through CRAC channels. It is unclear how abnormal ion flow leads to tubular aggregate myopathy. Evidence suggests that the tubular aggregates are composed of proteins that are normally part of the sarcoplasmic reticulum. Although the mechanism is unknown, some researchers speculate that the aggregates are the result of uncontrolled calcium levels in muscle cells, possibly due to abnormal STIM1 activity.

Researchers are not sure why another gain-of-function mutation causes the additional signs and symptoms of Stormorken syndrome.

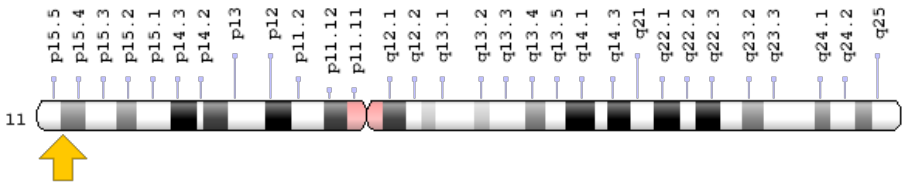
other disorders

At least three mutations in the *STIM1* gene cause an immune system disorder called primary immunodeficiency 10. Because of immune system problems, individuals with this condition have recurrent infections that can be life-threatening. The mutations that cause primary immunodeficiency 10 are known as "loss-of-function" mutations because they reduce or eliminate the function of the STIM1 protein. Without stimulation by STIM1, calcium ion flow through CRAC channels is impaired, which hinders the ability of immune system cells to fight infections.

Chromosomal Location

Cytogenetic Location: 11p15.4, which is the short (p) arm of chromosome 11 at position 15.4

Molecular Location: base pairs 3,855,703 to 4,093,210 on chromosome 11 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- D11S4896E
- GOK
- IMD10
- STRMK
- TAM
- TAM1

Additional Information & Resources

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28STIM1%5BTI%5D%29+OR+%28stromal+interaction+molecule+1%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- IMMUNODEFICIENCY 10
  http://omim.org/entry/612783
- STROMAL INTERACTION MOLECULE 1
  http://omim.org/entry/605921

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_STIM1.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=STIM1%5Bgene%5D
- HGNC Gene Family: Sterile alpha motif domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/760
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=11386
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/6786
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